What's New with Endoscopic Treatments for Early Gastric Cancer in the "Post-ESD Era"?

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Keywords

Early gastric cancer · Laparoscopic endoscopic cooperative surgery · Sentinel node navigation surgery · Endoscopic full-thickness resection · Endoscopic closure

Abstract

Background: Endoscopic treatments for gastric cancers have still been progressing even after the great success of endoscopic submucosal dissection (ESD). **Summary:** In further advancements of ESD, safe and less-invasive procedures are challenged by managing postoperative bleeding, one of the major adverse events in ESD. Covering the mucosal defect after removal of lesions appears reasonable and effective for preventing delayed bleeding from the post-ESD ulcers. Shielding with biodegradable sheets is attempted on clinical trials, which show equivocal results. Although suturing of the mucosal rims is technically challenging, pilot studies demonstrate favorable outcomes for avoiding post-ESD bleeding even in cases at high risk. In cases after noncurative resection of ESD, the selection of patients who truly require additional gastrectomy with lymph node dissection is important to provide necessary surgery. Risk stratification of lymph node metastases and surgery has been developed,

which offers tailor-made management to each patient considering the risks and benefits. In surgery, function-preserving gastrectomy to minimize the resection area in both lymphadenectomy and the primary site is clinically introduced. The sentinel node navigation surgery is promising to realize the minimally invasive gastrectomy, and it should strongly fit ESD as well as laparoscopic endoscopic cooperative surgery or endoscopic full-thickness resection, although nonexposure approaches are desirable. **Key Message:** Development for less-invasive managements on gastric cancer will be continued in step with the advancement of endoscopic treatments.

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Introduction

Endoscopic submucosal dissection (ESD) was born as a derivative of endoscopic mucosal resection in the late 1990s, removing a large lesion en bloc without limitation of the size of a snare. As dedicated electrocautery knives and high-frequency electric generators were developed, it had been established and permeated as less-invasive curative treatment for possible node-negative early gastric

cancer (EGC) both domestically and internationally in the 2000s. Subsequently, the indication of this borderless resection technique was expanded to lesions on other tracts: esophagus, colorectum, and even the duodenum.

ESD is helpful for patients in terms of preserving the stomach, but technically challenging for endoscopists, and therefore worth mastering. It seems that the enthusiasm for ESD has more or less stagnated the development on endoscopic treatment, as though ESD attracted many endoscopists too much to make further advancements. Accordingly, no epoch-making endoscopic treatment having a great impact comparable to ESD has been generated so far. Nevertheless, several novel approaches for the treatment of gastric cancers are proposed. In this mini review, the latest topics regarding endoscopic management of EGCs in this “post-ESD era,” from viewpoints of establishment of safe ESD, managements on noncurative ESD, and expansion of endoscopic intervention for gastric cancers.

What's Further Advancement of ESD?

The ESD procedure has been technically established, and the clinical utility of long-term outcomes is also confirmed. Based on reliable evidence, the indication of ESD has been expanded [1–4]. In the latest guidelines on gastric cancer treatments [5], differentiated-type intramucosal cancers >2 cm, differentiated-type intramucosal cancers with ulcerative findings 3 cm or less, and undifferentiated-type intramucosal cancers 2 cm or less, that are previously treated as expanded indications, have been included in the absolute indication. When these lesions are removed en bloc with negative tumor margins and no angiolymphatic infiltration, it is considered that curative resection is obtained.

One of the unsolved issues regarding the establishment of safe ESD is prophylaxis against post-ESD bleeding, particularly patients at high risk of bleeding, for example, having antithrombotic agents (ATAs). In mega data analyses [6], the risk of post-ESD bleeding involves 5% and is increased according to the accumulation of influential factors, for example, use of anticoagulants, chronic kidney disease on hemodialysis, use of antiplatelet agents, numbers of lesion removed, size, location, etc. The timing of bleeding has bimodal peaks [7], and rebleeding can occur in the patients with large lesions or warfarin usage [8]. Several countermeasures on postoperative bleeding have been proposed and routinely introduced in clinical settings: post-ESD coagulation (prophy-

lactic vessel coagulation on mucosal defects after the resection) [9] and perioperative use of antisecretory agents [10]. However, post-ESD bleeding does occur, and the rate of delayed bleeding raises up to approximately 30% in high-risk cases [7, 11, 12]. As the society is mature and the aging population is increased, the patients having ATAs are also increasing [13]. Therefore, the prevention of postoperative bleeding after ESD is an urgent matter to be addressed.

The cause of post-ESD bleeding lies in the exposure of mucosal defects after the removal of lesions. It is considered that in addition to neovascularization along with the mucosal healing, various stimuli by peristalsis, gastric acid, or food induce bleeding from the surface of the mucosal defects. Therefore, covering the defects will be reasonable to avoid these stimuli. Shielding with biodegradable sheets, for example, a polyglycolic acid sheet, and fibrin glue seems accessible due to the availability of materials used. This technique will also be helpful to avoid postoperative deformity of the stomach to bridge the defects. A pilot study demonstrated that this technique was useful for preventing post-ESD bleeding [14], whereas a succeeding randomized controlled study failed to provide favorable results [15], mainly due to the selection of cases. Furthermore, once bleeding occurred, endoscopic hemostasis appears difficult because of the existence of the sheet. Further investigation is expected to establish such covering methods.

Another approach on the prevention of post-ESD bleeding is the closure of the mucosal defect. This concept is, however, challenging as more than expected. First, the defect closure is technically difficult by using endoscopic clips, which is the most familiar device for tissue apposition [16]. For the closure of large defects, purse-string closure with a detachable snare and clips is feasible, although it will finish a tentative closure [17]. Second, even though the defect is closed, it is easily dehiscence in a short period. Therefore, the defect closure requires long-lasting apposition of the mucosal rims. Recently, several endoscopic suturing techniques were devised along with the development of advanced endoscopic treatments and have been clinically applied to mucosal defects after gastric ESD. The Overstitch™ suturing system (Apollo Endosurgery, Inc., Austin, TX, USA) [18], the double-armed bar suturing system [19], and endoscopic hand-suturing (EHS) by using the through-the-scope type flexible needle holder (Olympus Co., Ltd., Tokyo, Japan) [20–22] are expected to provide reliable closure of the mucosal defect after ESD and hopefully to decrease the risk of postoperative bleeding even in high-risk patients of bleeding

Fig. 1. EHS for the prevention of bleeding after ESD. **a** A mucosal defect is created on the lesser curvature on the upper third of the stomach. **b** In a retroflex view, mucosal rims are linearly sutured by using the through-the-scope type needle holder and an absorb-

able barbed suture thread. **c** The mucosal defect is completely closed. **d** On the postoperative day 3, the defect remains closed. ESD, endoscopic submucosal dissection; EHS, endoscopic hand-suturing.

Table 1. Outcomes of EHS for mucosal defects after gastric ESD in the previous pilot studies

Lesions, <i>n</i>	60
Patients, <i>n</i>	58
Patients with ATAs [†] , % (<i>n</i> / <i>N</i>)	60 (35/58)
Complete closure rate, % (<i>n</i> / <i>N</i>)	98 (59/60)
Closure maintenance rate [‡] , % (<i>n</i> / <i>N</i>)	85 (51/60)
Major bleeding rate, % (<i>n</i> / <i>N</i>)	5 (3/58)

[†] ATAs, antithrombotic agents (continued perioperatively in all patients); EHS, endoscopic hand-suturing; ESD, endoscopic submucosal dissection. [‡] Endoscopy was performed on the postoperative day 3 or 7.

(Fig. 1). Although these suturing techniques are limited use, and clinical cases of endoscopic suturing for the post-ESD mucosal defects are still small, EHS has had the largest number of cases so far. In previous 3 studies, 60 post-ESD defects in 58 patients including 35 patients with continuous administration of ATAs were sutured by using the EHS technique, which demonstrated favorable results in the technical feasibility and the usefulness for preventing delayed bleeding (Table 1).

Furthermore, the application of the post-ESD defect closure in patients at low risk of bleeding will also be meaningful in terms of shortening of hospitalization period because hospitalization is required mainly to prepare for possible postoperative bleeding. Therefore, if the secure defect closure decreases the risk of delayed bleeding,

the intensive care by hospitalization will become unnecessary, and ESD as day surgery may be realized in the future. Although several disadvantages and concerns are considered: long procedure time, additional medical costs, and difficulty in performing subsequent ESD for marginal lesions of the mucosal defect, particularly at the early phase after the suturing, the establishment of endoscopic mucosal closure method is expected for less-invasive ESD.

No Surgery, No Prognosis after Noncurative ESD?

As mentioned above, the indication of ESD has been expanded due to the accumulation of evidence on long-term outcomes. In contrast, the management of patients with noncurative ESD (endoscopic curability C-2 according to the current Japanese guideline [5]) remains one choice, surgery, because the risk of lymph node metastases exists and eradication of possibly cancer-positive lymph nodes is mandatory to obtain curative resection. However, the rate of lymph node metastases in surgical specimens is low, which indicates that most patients are losing the cancer-negative stomach and surrounding tissues, including lymph nodes, vessels, and nerves. Therefore, observation without surgery can also be a practical option, particularly in elderly patients. Previous articles elucidate that more than half of elderly patients has opted no surgery [23–26].

To decrease the number of patients having postgastrectomy syndrome due to unnecessary surgery, it is important to efficiently select the patients who should undergo additional surgery. Hatta et al. [27] introduced the risk scoring system of possible lymph nodes by assessing the massive number of noncurative ESD cases. They investigated the degree of relevance in several influential factors on lymph node metastases and scored each factor as follows: 3 points in the lymphatic invasion; 1 point in size (>3 cm), positive vertical margin, venous invasion, and submucosal invasion ($\geq 500 \mu\text{m}$). By summing these scores, the risk of lymph node metastases can be estimated: 2.5% (0–1 point), 6.7% (2–4 points), and 22.7% (5–7 points). By using this “eCura system,” a favorable clinical course can be recommended in each individual case.

However, it is still difficult to determine whether patients with noncurative ESD should undergo additional surgery from the aspect of lymph node metastases risk only because the patient’s factors, for example, comorbidities, life expectancy, and tolerability for surgery, should also be considered. Sekiguchi et al. [26] investi-

gated the clinical outcomes of ESD in patients aged 85 years or more and demonstrated that the prognostic nutritional index (PNI), one of the indicators of nutrition estimated by the serum albumin concentration and the total lymphocyte count, was a significant prognostic factor on the high-aged cohort. They concluded that the indication of ESD should be reconsidered in elderlies with low prognostic nutritional index. The Charlson comorbidity index, which is also a risk score considering comorbid conditions, appears to be useful to predict mortality after ESD, particularly in patients who underwent noncurative ESD [28–30].

This concept implies that additional surgery is not beneficial but rather harmful in these patients with noncurative ESD. Practically, several observational studies show that the overall survival is shorter in noncurative ESD patients without additional surgery than in patients with surgery whereas the disease-specific survival has no difference between the 2 groups [31], although these results are obtained with a strong selection bias. Therefore, the indication of additional surgery should be individually determined considering the patient’s status.

Surgical risk accompanied by additional gastrectomy can be calculated using multivariate analyses of influential factors on perioperative complications. The “Risk Calculator” is a spin-off system derived from big data of surgery in Japan termed the National Cancer Database [32]. On the web system, the surgical risk of gastrectomy (distal gastrectomy or total gastrectomy), for example, pneumonitis, perioperative death, anastomotic leak, is indicated by filling in the required fields regarding the patient’s clinical conditions. When a patient with noncurative ESD has several comorbidities that may increase the surgical risk of additional gastrectomy, the risk calculation would be of help to recommend an optimal treatment.

What Are Post-ESD Endoscopic Interventions?

In gastrectomy with lymphadenectomy for possible node-positive EGCs, minimizing the dissection area of lymph nodes and the resection area of the stomach is being attempted by introducing the sentinel node concept. This concept is that when the sentinel nodes, defined as the first drainage nodes from the primary site, are tumor-negative, subsequent nodes at the downstream of the lymphatic flows can also be considered as tumor-negative. The sentinel node navigation surgery (SNNS) based on this theory has already been introduced in the field of

Fig. 2. Current status on the developments of endoscopic treatment for gastric cancers after the establishment of ESD. Beyond the step of establishment of ESD, 3 directions of the development are indicated: further development for safe and less-invasive ESD,

stratification of patients requiring surgery, and expansion of endoscopic intervention. ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; LECS, laparoscopic and endoscopic cooperative surgery.

malignant melanoma or breast cancer, and its utility is clinically demonstrated. In the surgical scene of gastric cancers, this concept is being introduced in several leading institutions as clinical research or advanced medical treatment. In a multicenter, prospective study regarding the applicability of SNNS for preoperatively diagnosed EGCs, the accuracy of evaluation for metastasis based on the sentinel node concept was 99% [33]. In an ongoing randomized controlled trial on the utility of SNNS for EGCs, the Korean research group presented the short-term outcomes, which demonstrated that organ-preserving surgery was performed in 81.4% with postoperative complications in 15.5% [34]. They concluded that SNNS for EGCs was feasible and as safe as laparoscopic standard gastrectomy as control.

According to the previous study, a reasonable indication of gastric SNNS in Japan is considered cT1N0M0 single gastric cancer of <4 cm in size. When SNNS is established and clinically permeated as one option of less-invasive, function-preserving surgery in EGCs, endoscopic resection for a primary lesion will be helpful as a least-invasive resection method for a primary lesion. This attempt has been introduced at leading institutions of SNNS. In the combination of SNNS with ESD, a pilot study on simultaneous resection of a primary site and sentinel node basin dissection was reported in 2012 [35]. Subsequently, to focus the application of SNNS on possible node-posi-

tive cancers, SNNS after noncurative ESD was introduced, and a phase II trial to evaluate the feasibility of this concept is currently ongoing in Korea [36]. However, in the resection of possible node-positive EGCs that include cancers deeply invaded into the submucosa, full-thickness resection would be preferable to avoid incomplete resection. Furthermore, nonexposure technique is desired to remove cancers without a potential risk of cancer cell seeding into the abdominal cavity [37]. Several nonexposure methods have been developed as related techniques to laparoscopic and endoscopic cooperative surgery. Non-exposed endoscopic wall-inversion surgery (NEWS), which involves laparoscopic sero-muscular incision around a lesion and subsequent sero-muscular suturing, followed by endoscopic mucosal incision around the inverted lesion. A clinical introduction of NEWS with SNNS has been reported as a promising minimally invasive treatment for possible node-positive EGCs [38]. Korean group conducted the feasibility study of this concept by using a modified NEWS technique, which demonstrated acceptable results but also revealed technical difficulties in obtaining R0 resection and avoiding perforation [39]. Okubo et al. [40] introduced another nonexposed laparoscopic and endoscopic cooperative, a combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique, combined with SNNS, which demonstrated favorable results in terms of both technical

success and preservation of patients' better quality of life. Along with the acceptance of SNNS in EGCs and accumulation of cases, endoscopic resection with SNNS will be further developed in the future.

Endoscopic full-thickness resection (EFTR), which means pure endoscopic local resection involving circumferential mucosal incision and subsequent sero-muscular incision followed by endoscopic defect closure, is being developed for gastric subepithelial tumors [41]. This technique is still challenging in terms of secure removal of the lesion and secure closure of the full-thickness defect. The indication should also be limited to subepithelial lesions considering a potential risk of cancer seeding as mentioned above. Furthermore, gastric cancers as a candidate for EFTR are currently difficult to find because possible node-negative cancers are removed by ESD and possible node-positive ones require gastrectomy with lymph node dissection. Accordingly, in patients having submucosally invading cancer as well as high risk of gastrectomy, EFTR might be acknowledged as suboptimal treatment in the future, although risks and benefits should be carefully considered. Even though the introduction of EFTR to gastric cancers is accepted, advanced EFTR, such as sealed EFTR [42], would be desirable to minimize the demerits of this treatment option.

Future Perspectives

Current progresses on endoscopic treatment of gastric cancers appear small but steady, particularly to further pursue less-invasiveness (Fig. 2). ESD will become a

safer and short-hospitalization procedure by addressing countermeasures for postoperative bleeding. The number of patients who undergo additional gastrectomy will be decreased as the risk balance between surgery and observation is further clarified. In cases of additional surgery, endoscopic intervention may be helpful to provide minimally invasive gastrectomy. As *H. pylori* eradication is permeated, characteristics of gastric cancers will also be changed, hopefully small-sized and indolent. In this situation, gastric cancers will be more treatable and suitable for endoscopic treatments. Further advancements are expected for the eradication of gastric cancers in the future.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

O. Goto substantially contributed to the conception or design of the work and drafted the work. M. Kaise revised it critically for important intellectual content. K. Iwakiri performed the final approval of the version to be published.

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